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10/770,291	02/02/2004	Yihong Qiu	6437.US.C5	2213

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
06/23/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/770,291	QIU ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The receipt is acknowledged of applicants' amendment filed 03/18/2008.

Claims 1-5, 17, and 18-19 have been canceled.

Claim 16 is pending and included in the prosecution.

The following new ground of rejection is necessitated by applicants' amendment:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for very specific oral formulations having specific ingredients to deliver divalproex sodium, does not reasonably provide enablement for any pharmaceutical formulation comprising any valproate compounds as currently recited by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the breadth of the claims; the state of the prior art; the relative skill of those in the art; the amount of direction or guidance presented; the predictability or unpredictability of the art; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention: The nature of the invention as claimed is: an oral hydrophilic matrix formulation comprising divalproex sodium for once a day administration.

The breadth of the claims: The claims are broad. The claims encompass myriad of oral hydrophilic matrix formulations comprising divalproex sodium.

The state of the prior art: The state of the art recognizes once a day oral administration of divalproex sodium in a pharmaceutical formulation, see US 4,913,906, however, the art does not recognize the formulation that provides the claimed dissolution profiles.

The amount of direction or guidance presented: The specification provides no guidance, in the way written description, on any oral hydrophilic matrix formulations other than oral formulation that provides the claimed dissolution profile that is provided by example 1. In page 6, applicants disclosed the claimed dissolution profile, and stated that "Upon

ingestion, a formulation meeting this profile produced C_{max}, C_{min}, and AUC describe above". This disclosure emphasizes that the claimed dissolution profile is obtained by specific oral administration of the hydrophilic matrix. In example 1, pages 20-22, applicants disclosed very specific oral hydrophilic matrix formulations containing divalproex sodium as shown by table 4 at page 27, and this specific formulation provides the specific claimed dissolution profile. However, instant claims do not recite any specific hydrophilic matrix formulation and only require "hydrophilic oral matrix", which includes any and all possible oral hydrophilic matrix formulations. While it is conceivable that art known oral hydrophilic matrix formulations are capable of providing the claimed dissolution profile, the matrix materials are virtually limitless in the art and there is nothing in the specification that equates or correlates that all of the art known hydrophilic matrices are similar and that all of them result in the same dissolution profile for divalproex sodium as claimed in the instant application. In the absence of any guidance regarding oral formulation other than specific hydrophilic matrix formulation, a practitioner would turn to trial and error experimentation in testing every known oral formulation in order to compose oral formulation to deliver divalproex sodium having the claimed delivery profile, with any and all known oral formulations, so as to achieve the claimed profiles. It is not obvious from the disclosure of specific oral hydrophilic matrix tablet formulation comprising specific ingredients in specific amounts containing specific amount of divalproex sodium if all other matrix formulations will work to provide the same dissolution profile. The claimed dissolution profile is the result of the described specific hydrophilic matrix formulation. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ

radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result. A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the formulations fall within the scope of a claim will possess the alleged activity. See *In re Riat et al.* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr et al.* (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The predictability or unpredictability of the art: The lack of guidance from the specification and from the prior art with regard to formulations comprising divalproex sodium and provides the claimed dissolution profile makes practicing the claimed invention unpredictable in the terms of determining hydrophilic matrix formulations other than the disclosed formulation.

The presence or absence of working examples: The specification discloses only very specific oral hydrophilic matrix formulation comprising divalproex sodium, pages 6, 12, and example 1. No working examples to show formulations other than the disclosed oral hydrophilic matrix formulation. Therefore, the specification has enabled only specific oral hydrophilic matrix formulations having specific ingredients to deliver divalproex sodium to provide the claimed dissolution profiles.

The quantity of experimentation necessary: The specification demonstrates one oral hydrophilic matrix formulation of divalproex sodium. Therefor, the practitioner would turn to trial and error experimentation to practice the instant composition to delivering other hydrophilic matrix formulations that provides the required dissolution profile without guidance from the specification or the prior art. Therefore, undue

experimentation becomes the burden of the practitioner. The quantity of experimentation required in the instant case is undue because there is a substantial gap between very one specific oral hydrophilic matrix formulation, and any other oral hydrophilic matrix formulation that results in the claimed dissolution profile. As stated earlier, oral hydrophilic matrix formulations comprise huge list of compounds. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

The following rejections have been discussed in the previous office action, and are maintained for reasons of record:

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,419,953. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed dissolution profile is inherent.

5. Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,511,678. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed dissolution profile is inherent.

6. Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,528,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed dissolution profile is inherent.

7. Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,528,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed dissolution profile is inherent.

8. Claims 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,720,004. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed dissolution profile is inherent.

9. Claim 16 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,713,086. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed dissolution profile is inherent.

10. Claim 16 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 46-59 of copending Application No. 10/770,290. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the referenced copending applications and would be covered by any patent granted on the copending applications since the referenced copending applications and the instant application are claiming common subject matter as follows: formulation comprising valproate compounds. The present claims and the conflicting claims in the copending application anticipate each other since pharmacokinetics and dissolution profile are inherent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

11. The examiner acknowledges applicants intention to hold double patenting rejections in abeyance until notification of allowable subject matter to file the appropriate terminal disclaimers to obviate the above rejections. Therefore, double patenting rejections are maintained. Regarding the provisional double patenting rejection, the rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only remaining rejection

in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other applicant into a double patenting rejection at the time the one application issues as a patent.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by article "EPILIM CHRONO: A MULTIDOSE, CROSSOVER COMPARISON OF TWO FORMULATIONS OF VALPROATE IN HEALTHY VOLUNTEERS", by Roberts et al.

> The present claims are directed to oral hydrophilic matrix formulation comprising divalproex sodium administered once a day.

Roberts et al. disclosed once a day controlled release formulation to deliver divalproex sodium: Epilim Chrono. Epilim Chrono comprises valproate compounds and hydrophilic polymer "ethylcellulose as evident by patient information leaflet of the product. Epilim Chrono is also in the form of a matrix formulation because matrix, as defined by applicants in page 12, "the drug is homogeneously dispersed in the polymer". Roberts et al. provided comparison between once a day formulation and twice

daily controlled formulation. The comparison showed once a day formulation of 1000 mg is almost identical to the enteric coated twice a day formulation. The dissolution profile is inherent to a specific formulation.

Response to Arguments

14. Applicant's arguments filed 03/18/2008 have been fully considered but they are not persuasive.

Applicants argue that Roberts et al. disclose an investigation that compared the steady state pharmacokinetics and relative bioequivalence of a mixture of sodium valproate and valproic acid administered twice daily (500 mg Epilim® Chrono b.d.) or once daily (1000 mg Epilim® Chrono o.d.) and an enteric coated tablet containing only sodium valproate administered twice daily (500 mg Epilim® EC b.d) (See page 176). The study concluded that the once-daily Chrono regimen was bioequivalent to the twice-daily EC and Chrono formulations with respect to AUC, that the half-life was more or less identical and that the Cmin and Cmax at steady state for the once-daily Chrono were almost identical to those for the twice-daily EC regimen.

In response to these arguments, it is noted that the set forth Applicants' statement regarding Robert's teachings admits that the Robert et al. disclosed once a day dose comprising sodium valproate. Once a day formulation comprising valproate sodium was known at the time of the invention, and was disclosed by Robert to be superior and more effective over twice a day formulation. The pharmacokinetics disclosed by Robert et al. are the same as instantly claimed. In absence of claiming a

specific formulation, the formulation disclosed by Robert meets the claims. The present claims' language "comprising" permits the presence of other valproate compounds in the oral formulation.

Applicants argue that Roberts et al. do not disclose an oral hydrophilic matrix formulation that contains sodium valproate that can be administered once per day. The sodium valproate composition described by Roberts et al. is administered twice daily.

In response to this argument, it is argued that Roberts et al. disclosed once a day controlled release formulation to deliver divalproex sodium: Epilim Chrono. Epilim Chrono comprises valproate compounds and hydrophilic polymer "ethylcellulose as evident by patient information leaflet of the product. Epilim Chrono is also in the form of a matrix formulation because matrix, as defined by applicants in page 12, "the drug is homogeneously dispersed in the polymer". Hence, Robert clearly disclosed hydrophilic matrix oral formulation as instantly claimed.

Applicants argue that Roberts et al. does not disclose or suggest the claimed in-vitro dissolution profile. Applicants argue that the Examiner has not met her burden of establishing that the Roberts et al. formulations would have inherently the same dissolution profile as the claimed formulation. The Examiner has failed to provide any extrinsic evidence to establish that the formulations of Roberts et al. would necessarily have the same dissolution profile as the claimed formulation. It is also well known that inherency cannot be established by probabilities or possibilities.

In response tot his argument, it is argued that the release rate and plasma levels are inherent for specific formulation, See Atlas Powder versus Ireco, 51 USPQ 2d 1943, (Fed. Cir. 1999), holds the failure of those skilled in the art to contemporaneously recognize an inherent property, function, or ingredient of a prior art reference does not preclude a finding of anticipation. Whether or not an element is inherent in the prior art is a fact question. Inherency is not necessarily conterminous with knowledge of those of ordinary skill in the art, who may not recognize the inherent characteristics or functioning of the prior art. However the discovery of a previously unappreciated property of a prior art composition does not render the old composition new to the discoverer. The fact that prior art taught away from the claim is, in fact, only a showing that prior art did not recognize the inherent function. This lack of contemporary understanding did not defeat the showing of inherency. The present claim is directed to product, which is oral hydrophilic matrix formulation for once a day administration comprising divalproex sodium and polymer, which is identical to the product disclosed by Robert and inherently will have the same dissolution profile. It has been held that once a reference teaching product appearing to be substantially identical is made basis of rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to applicant to show an unobvious difference. The PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same. The burden of proof is

similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

15. Claims 16 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by US 4,913,906 ('906).

US '906 disclosed composition for controlled release of salts of valproic acid comprising 10-80% of the active agent (abstract; col.2, lines 1-10, 63-68). The controlled release formulation results in sustained action of the drug with small fluctuation of the plasma level over prolonged period of time (col.1, lines 59-62). The composition is a once a day oral formulation that delivers the drug for 24 hour and shows about 97% dissolution rate profile after 24 hr. (col. 5 and 6, tables 1-4). Divalproex sodium is disclosed as one of the salts of valproic acid suitable for the formulation of the reference (col.5, lines 15-20). The dissolution profile is inherent for the formulation. In absence of claiming a specific formulation, the prior art anticipated the claims.

Response to Arguments

16. Applicant's arguments filed 03/18/2008 have been fully considered but they are not persuasive. Applicants argue that no pharmacokinetic data for divalproex sodium is provided. Applicants repeat the argument regarding inherency.

In response to this argument, it is argued that once day formulation comprising valproate sodium was known at the time of the invention, as disclosed by US '906. US '906 disclosed sustained action of once a day oral formulation with small fluctuation of the plasma level over prolonged period of time that delivers the drug for 24 hour and shows about 97% dissolution rate profile after 24 hr. In absence of claiming a specific formulation, the formulation disclosed by US '906 meets the claims. The present claims' language "comprising" permits the presence of other valproate compounds.

The examiner herby repeats the argument regarding inherency as in section 14 as set forth in this office action.

Conclusion

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Isis A Ghali/
Primary Examiner, Art Unit 1611

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